Title

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Journal

Gastroenterology, 161(5)

ISSN

0016-5085

Authors

Mehta, Neil
Frenette, Catherine
Tabrizian, Parissa
et al.

Publication Date

2021-11-01

DOI

10.1053/j.gastro.2021.07.033

Peer reviewed

HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Gastroenterology. 2021 November ; 161(5): 1502–1512. doi:10.1053/j.gastro.2021.07.033.

Down-staging Outcomes for Hepatocellular Carcinoma: Results from the Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) Consortium

Neil Mehta[1], **Catherine Frenette**[2], **Parissa Tabrizian**[3], **Maarouf Hoteit**[4], **Jennifer Guy**[5], **Neehar Parikh**[6], **T. Tara Ghaziani**[7], **Renu Dhanasekaran**[7], **Jennifer L. Dodge**[8], **Brahma Natarajan**[1], **Matthew L. Holzner**[3], **Leana Frankul**[2], **Wesley Chan**[1], **Austin Fobar**[6], **Sander Florman**[3], **Francis Y. Yao**[1,8]

[1]Division of Gastroenterology, Department of Medicine, University of California, San Francisco

[2]Center for Organ and Cell Transplantation, Scripps Green Hospital

[3]Department of Surgery, Icahn School of Medicine at Mount Sinai, New York

[4]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania

[5]Department of Transplantation, California Pacific Medical Center

[6]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan

[7]Division of Gastroenterology and Hepatology, Stanford University, Palo Alto, California

[8]Division of Transplant Surgery, Department of Surgery, University of California, San Francisco

Abstract

Background/Aims: United Network of Organ Sharing (UNOS) has adopted uniform criteria for down-staging (UNOS-DS) of hepatocellular carcinoma (HCC) prior to liver transplantation (LT), but down-staging success rate and intention-to-treat outcomes across broad geographic regions are unknown.

Corresponding Author: Neil Mehta, M.D., University of California, San Francisco, 513 Parnassus Avenue, Room S-357, San Francisco, CA 94143-0538. Tel: (415)-502-2569, Fax: (415)-476-0659, neil.mehta@ucsf.edu.

Author Contributions:

Concept and design: Mehta, Yao

Acquisition, analysis, or interpretation of data: Mehta, Frenette, Tabrizian, Hoteit, Guy, Parikh, Ghaziani, Dhanasekaran, Dodge, Holzner, Frankul, Chan, Fobar, Yao

Drafting of the manuscript: Mehta, Dodge, Yao

Criticial revision of the manuscript for important intellectual content: Frenette, Tabrizian, Hoteit, Guy, Parikh, Ghaziani, Dhanasekaran, Natarajan, Holzner

Statistical Analysis: Mehta, Dodge, Yao

Supervision: Florman, Yao

Methods: In this first multi-regional study (7 centers, 4 UNOS regions), consecutive patients with HCC undergoing down-staging based on UNOS-DS criteria were prospectively evaluated from 2016–2019 (n=209).

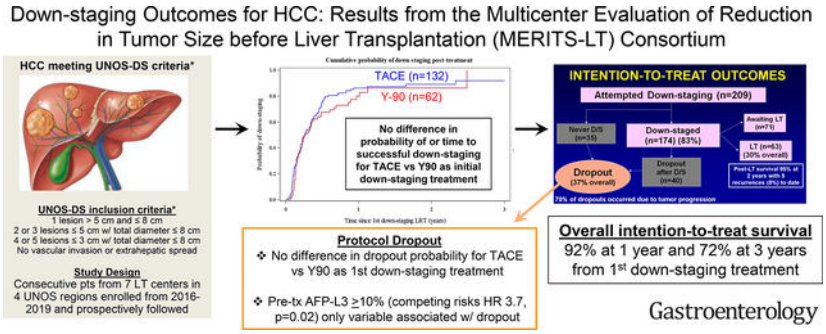
Results: Probability of successful down-staging to Milan criteria and dropout at 2 years from initial down-staging procedure was 87.7% and 37.3%, respectively. Pre-treatment AFP-L3 ≥10% (HR 3.7, p=0.02) was associated with increased dropout risk. When comparing chemoembolization (n=132) and Y-90 radioembolization (n=62) as initial down-staging treatment, there were no differences in mRECIST response, probability of or time to successful down-staging, waitlist dropout or LT. Probability of LT at 3 years was 46.6% after a median of 17.2 months. In the explant, 17.5% had vascular invasion and 42.8% exceeded Milan criteria (under-staging). The only factor associated with under-staging was the sum of the number of lesions plus largest tumor diameter on last pre-LT imaging, and odds of under-staging increased by 35% per 1 unit increase in this sum. Post-LT survival at 2 years was 95% and HCC recurrence occurred in 7.9%.

Conclusion: In this first prospective multi-regional study based on UNOS-DS criteria, we observed successful down-staging rate of >80%, and similar efficacy of chemoembolization and Y-90 radioembolization as initial down-staging treatment. A high rate of tumor under-staging was observed despite excellent 2-year post-LT survival of 95%. Additional LRT to reduce viable tumor burden may reduce tumor under-staging.

LAY SUMMARY

This prospective multi-regional study demonstrates >80% probability of down-staging with similar efficacy of TACE and Y-90 as initial treatment. This validates the feasibility of down-staging broadly under current UNOS guidelines.

Graphical Abstract



Keywords

alpha-fetoprotein (AFP); local regional therapy (LRT); tumor recurrence; waitlist dropout

INTRODUCTION

Liver transplantation (LT) is an ideal treatment option for early-stage hepatocellular carcinoma (HCC) because LT removes not only the tumor but also the oncologic potential

of the diseased liver. The number of HCC waitlist registrations in the United States has risen considerably in the past 2 decades, and HCC now accounts for nearly 30% of all LT performed in the United States (1, 2). The Milan criteria for LT (3) remain the gold-standard for candidate selection in the United States, although they are considered by many to be too restrictive and a plethora of expanded criteria have been proposed over the years (4–7). The use of more liberal criteria, however, may result in higher tumor recurrence rates and reduce access to LT for other patients with a better prognosis (8, 9). Additionally, expanded criteria does not account for the effects of local regional therapy (LRT), which is increasingly used to control tumor growth when the waiting time is prolonged, and also serves as a tool to improve candidate selection (10). Regardless of whether the tumor stage is within or beyond Milan criteria, objective response to LRT has been shown to be a marker of favorable tumor biology whereas tumor progression despite LRT reflects aggressive tumor behavior associated with a greater propensity for tumor recurrence after LT (11–14).

Tumor down-staging, defined as a reduction of viable tumor burden by LRT to meet acceptable LT criteria, has garnered support in recent years as a better alternative to simply expanding the tumor size limits for LT (6, 7, 15, 16). In essence, down-staging aims at merging expanded criteria with response to LRT, serving as a tool to select a subset of patients with favorable tumor biology who would respond to down-staging treatments and also do well after LT (15). The University of California, San Francisco (UCSF) group published the largest single-center experience with tumor down-staging using a uniform protocol with well-defined inclusion criteria (17). Those successfully down-staged to within Milan criteria had a 5-year post-LT survival of 78% and a tumor recurrence rate of 8%, similar to those initially meeting Milan criteria not requiring down-staging (17). A subsequent study from United Network of Organ Sharing (UNOS) Region 5 involving 3 centers (18) using the same down-staging protocol showed similar results, with a 5-year post-LT survival of 80% and post-LT recurrence rate of less than 15%. Despite these encouraging results, a pooled analysis of all published series on tumor down-staging demonstrated a wide range of down-staging success rates from 11% to 77% and tumor recurrence rates from 7 to 33% (16). The substantial variations in these outcomes may be explained by the heterogeneity of the study populations and lack of strict inclusion criteria in most studies.

As many LT centers began to employ tumor down-staging strategies for LT, staging definitions and endpoints varied widely across regions (19). In an effort to standardize criteria for down-staging, UNOS/OPTN (Organ Procurement and Transplantation Network) adopted the UCSF/Region 5 down-staging protocol in 2017 (hereafter referred to as UNOS-DS) as a national policy, whereby patients meeting the UCSF/ Region 5 inclusion criteria and achieving successful down-staging to within Milan criteria are eligible to receive automatic priority listing with Model for End Stage Liver Disease (MELD) exception (20). The standardized application of down-staging has also provided the opportunity for large-scale prospective multicenter studies to validate the feasibility and efficacy of tumor down-staging, and to potentially refine selection or other staging criteria to further improve outcomes (19).

In this first prospective multi-center study on down-staging from the MERITS-LT consortium involving 7 centers from 4 UNOS regions, we aimed to examine the down-staging success rate and intention-to-treat outcomes based on uniform criteria (UNOS-DS protocol). We also sought to evaluate the influence of the type of initial down-staging treatments and other factors on the likelihood of successful down-staging.

METHODS

Down-staging Protocol and Radiographic Assessment

The UNOS down-staging protocol has previously been described in detail (17) and is summarized in Table 1, including eligibility criteria based on initial tumor size and number, and criteria for exclusion from LT. Consecutive patients from 7 high-volume LT centers with previous down-staging experience in 4 UNOS regions with HCC meeting UNOS-DS eligibility criteria were enrolled from 2016–2019 and prospectively followed. Three additional LT centers from two more UNOS regions eventually were unable to provide data so were removed from the consortium. A minimum follow-up of 6 months after the first down-staging treatment was required for inclusion. All imaging studies for enrolled patients were assessed using Liver Imaging Reporting and Data System (LI-RADS) criteria (21), which has been incorporated into the UNOS/OPTN guidelines (22). Percutaneous biopsy was not routinely performed for the diagnosis of HCC at any of the institutions and hepatic nodules <1 cm were not counted as HCC.

The specific type of LRT used was at the discretion of each of the center's multidisciplinary tumor boards and was not pre-specified in the down-staging protocol. All patients included in the down-staging protocol underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen 1 month after each LRT, and at a minimum of once every 3 months. Following LRT, radiographic assessment of tumor size was based on measurements of the maximum diameter of only viable tumors by multi-phase CT or MRI, and did not include the area of necrosis resulting from LRT (23). Imaging criteria for successful down-staging included a decrease in tumor size to within Milan criteria, or complete tumor necrosis with no contrast enhancement. Each center applied LRT with repetitive interventions if needed to achieve complete necrosis of all tumor nodules if possible. Following successful down-staging of HCC, patients at each center were listed with MELD exception after a mandatory minimum wait period of 6 months.

Histopathologic Analysis

In patients who underwent LT after successful down-staging, explant histopathologic features evaluated included tumor size, number of tumor nodules, histologic grade of differentiation (24), and the presence or absence of micro- or macro-vascular invasion. Pathologic tumor staging was based on the UNOS TNM staging system (25). The size and number of only viable tumors were considered in pathologic staging.

Outcomes

The primary outcome of interest was probability of and factors associated with successful down-staging and protocol dropout due to tumor progression or liver-related death with

the primary exposure being type of initial down-staging treatment. Secondary outcomes included probability of LT, post-LT survival, and HCC recurrence. For patients removed from the down-staging protocol for developing a medical contraindication to LT not related to liver disease, no longer interested in undergoing LT, or noncompliant with each center's transplant policies, follow-up was censored at the time of delisting or removal from the protocol.

Statistical Analysis

The date of first down-staging procedure was defined as time zero in all statistical analysis, except post-LT outcomes for which the date of LT was time zero. Chi-squared, Fisher's exact, or Mann-Whitney U tests were used to compare differences in participant characteristics by type of 1st LRT (i.e. transarterial chemoembolization (TACE) versus Yttrium-90 (Y-90) radioembolization). The cumulative probabilities of successful down-staging, post-LT outcomes (survival and HCC recurrence), and intention-to-treat survival were estimated using the Kaplan-Meier method and compared across subgroups using the log-rank test. The cumulative probability of waitlist outcomes (dropout and LT) were estimated while accounting for the competing risk of the other waitlist event. Cox regression assessed factors associated with successful down-staging were estimated as hazard ratios (HR). Fine and Gray competing risks regression estimated risk of dropout due to tumor progression or liver-related death as sub-hazard ratios (sHR). Variables with a p-value of <0.1 in univariable analysis were evaluated in bivariable models.

RESULTS

Exclusion from the Down-staging Protocol

Among 324 patients with tumor burden meeting UNOS-DS criteria, 115 (35.5%) were not considered for LT and thus excluded from the down-staging protocol. Of these, 45.2% and 38.3% were due to medical and psychosocial contraindications to LT, respectively. Patients with baseline alpha-fetoprotein (AFP) >1000 ng/ml and decompensated liver disease have exceedingly high risk of treatment failure and accounted for 13.0% of exclusions. Finally, 3.5% of exclusions were patients with a baseline bilirubin >4 as they were not considered candidates for trans-arterial therapy (17). The remaining 209 patients comprised the study cohort.

Baseline Characteristics and Local-regional Therapy

The baseline characteristics and details of LRT of the study cohort of 209 patients are presented in Table 2. Each center enrolled at least 12 patients with the two largest centers enrolling 68 (32.5% of the overall cohort) and 33 patients (15.8%). Median age of the cohort was 63 years (interquartile range (IQR) 58–67) and 85.2% were male. Caucasians comprised 60.0% of the cohort and Hepatitis C was the most common etiology of liver disease (59.8%). At the time of first down-staging procedure, median MELD was 9 (IQR 7–11), 75.5% were Child's class A, and 3.0% were Child's class C. Median initial total tumor diameter was 6.2 cm (IQR 5.6–7.3). There were 32.1% with a single lesion measuring 5.1–8 cm, 54.1% with 2–3 lesions, and 13.9% with 4–5 lesions. Median baseline AFP was 13 ng/ml (IQR 5–74) and 11.5% had a pre-treatment AFP ≥1000 ng/ml. Median

lectin-reactive alpha-fetoprotein (AFP-L3) was 10.3% (IQR 4.6–16.9). Distribution of LRT received included 21.1% undergoing a single procedure, 25.4% receiving two LRTs, and 22.0% requiring ≥5 LRTs. TACE was the most common LRT used with 80.9% receiving at least one such procedure, 40.2% receiving at least one Y-90 radio-embolization, and 28.2% receiving at least one ablation procedure.

TACE was the 1st LRT received in 132 patients (63.1%) with 62 patients initially undergoing Y-90 tumor treatment (29.7%). All centers performed both TACE and Y-90 though center-specific differences in type of 1st LRT were observed (p=0.001). When comparing baseline characteristics of these two 1st LRT groups (Table 3), median pre-treatment age and Child's class were similar but the TACE group had a higher proportion of males (92.4% vs 72.6%, p<0.001) and slightly higher median MELD score (p=0.04). Median total tumor diameter and pre-treatment AFP were similar but the TACE group was more likely to have multi-focal disease (75.8% vs 51.6%, p=0.003). Both groups had a median of 1 lesion (IQR 1–2) treated with initial LRT. Radiographic response by mRECIST criteria to 1st LRT was similar between groups (p=0.67) with partial response most common in both groups (TACE 52.3%; Y-90 48.4%) followed by complete response (TACE 28.0%; Y-90 27.4%). Median time from initial LRT to post-treatment imaging on which mRECIST response was assessed was slightly longer in the Y90 group compared to the TACE group (6.3 vs 4.3 weeks, p=0.03). Median number of total LRTs received in the TACE group was 3 (IQR 2–5) compared with 2 (IQR 1–3) in the Y-90 group (p=0.006).

Intention-to-treat Outcome

Tumor Down-staging—The intention-to-treat outcome related to attempted down-staging is summarized in Figure 1. Successful down-staging to within Milan criteria was achieved in 174 patients (83.3%) after a median of 2.6 months (IQR 1.3–4.8). Among them, 66.1% were down-staged after a single LRT while 33.9% required multiple treatments to achieve successful down-staging. The cumulative probability of successful down-staging to within Milan criteria from first down-staging procedure was 67.5% at 6 months, 83.0% at 1 year, and 87.7% at 2 years. In Cox regression models, the only factor associated with ability to achieve tumor down-staging was decreasing total tumor burden (HR 0.82 per cm, 95% CI 0.69–0.96, p=0.02). The probability of successful down-staging at 1 year from 1st down-staging treatment was 88.3% in those with total tumor diameter <6 cm compared to 81.0% for total tumor diameter >7 cm (p=0.02).

When comparing TACE and Y-90 as initial down-staging treatment, no statistically significant differences were observed in probability of or time to successful down-staging (Table 3 and Figure 2). Additionally, pre-treatment number of lesions, MELD score, Child's class, AFP, AFP-L3%, des-gamma carboxyprothrombin (DCP), and neutrophil to lymphocyte ratio (NLR) were not significant predictors of successful down-staging nor was number of LRT received.

Down-staging Protocol Dropout—Of the 174 patients who initially achieved successful down-staging, 95.4% were subsequently listed for LT. Down-staging protocol dropout occurred in 75 patients (35.9% of overall cohort), including 51 due to tumor progression

(68.0% of dropouts) and 9 due to liver-related death without LT (12.0%). In those with tumor progression, 56.8% had dropout after receiving HCC MELD exception and the remaining 43.2% were still in the initial 6 month wait period at the time of dropout. The median time from first down-staging treatment to dropout was 8.7 months (IQR 5.9–13.4). The cumulative probability of dropout from first down-staging procedure was 22.5% at 1 year and 37.3% at 2 years. In bivariable competing risks analysis, pre-treatment AFP-L3 ≥10% (sHR 3.7, 95% CI 1.27–10.79, p=0.02) was associated with increased dropout due to tumor progression or liver-related death even with separate adjustment for age or AFP. The probability of dropout within 3 years of 1st LRT was 48.5% in those with an AFP ≥100 ng/ml compared to 37.3% for AFP <100 (p=0.08). There were no statistically significant differences observed in probability of or time to dropout based on type of 1st LRT received (Table 3, Figure 3) and no center-specific differences in dropout were observed.

Explant Pathology and Tumor Staging—At last follow-up, 63 patients (30.1% of the entire cohort) had received LT and 71 patients (34.0%) were within Milan criteria and active on the waiting list (Figure 1). On the last imaging prior to LT in these 63 patients, 30 (47.6%) had no residual tumor identified and median sum of the largest viable lesion (cm) plus number of viable lesions was 1.6 (IQR 0–4.4). The median time from 1st down-staging treatment to LT was 17.2 months (IQR 11.1–24.3). Median time from successful down-staging to LT was 13.9 months and ranged from 9.6 months for the center with the shortest wait time to 17.3 months for the center with the longest wait time. Cumulative probability of LT at 1 and 3 years from first down-staging procedure was 9.7% and 46.6%, respectively. When comparing TACE and Y-90 as initial down-staging treatment, there were no observed differences in proportion receiving LT, time to LT, or AFP at LT (Table 3) and no center-specific differences in probability of LT were observed.

At time of LT, complete tumor necrosis from LRT (no residual tumors in explant) was observed in 23.8%. Tumor stage was within Milan criteria (T1/T2) in 33.3% and beyond Milan criteria (T3/T4) in 42.8% due to under-staging by pre-LT imaging. The latter group included one patient with macro-vascular invasion (T4b) and one with lymph node invasion (N1). Micro-vascular invasion was observed in 17.5%. Among patients with viable tumors, most had moderately-differentiated tumors (66.6%) with seven patients (14.6%) having poorly-differentiated tumor grade. There were no significant differences in explant histology based on type of 1st LRT received (Table 3) though Y-90 patients had a higher proportion with completely necrotic tumor(s) (30.8% vs 20.5%) and a lower proportion with both tumor beyond Milan criteria (23.1% vs 43.2%) and microvascular invasion (7.7% vs 20.5%) (all p >0.25). Overall, median RETREAT score (25) was 2 (IQR 1–3) with 8.1% having a RETREAT score of ≥5. RETREAT score was similar based on type of 1st LRT received (p=0.56).

On univariate logistic regression analysis, the only factor associated with explant under-staging to beyond T2/Milan criteria was the sum of the number of lesions plus largest tumor diameter on the last imaging prior to LT. The odds of under-staging increased by 35% per 1 unit increase in this sum (OR 1.35, 95% CI 1.07–1.73, p=0.01). Type of initial LRT, mRECIST response to initial LRT, type of last imaging prior to LT (i.e. MRI vs CT), pre-LT AFP and NLR both as continuous variables and at all tested cutoffs (AFP >20

and >100 ng/ml; NLR >5), and transplant center were not significant predictors of explant under-staging on univariate analysis.

Factors associated with complete tumor necrosis in the explant using univariate logistic regression were pre-LT AFP <20 vs >20 ng/mL (OR 11.6, p=0.007) and the sum of the number of lesions plus largest tumor diameter on the last imaging prior to LT (OR 0.72 per 1 unit increase, p=0.04). Among those with no viable tumor on last imaging prior to LT, 32.1% had complete tumor necrosis compared to 12.9% of those with suspected viable tumor on last imaging (univariate logistic regression OR 3.13, p=0.14). Type of initial LRT, mRECIST response to initial LRT, type of last imaging prior to LT, pre-LT NLR, and transplant center were not associated with complete tumor necrosis in the explant.

Post-transplant Survival, HCC Recurrence, and Intention-to-treat Survival— Among the 63 patients who underwent LT, median post-LT follow-up was 1.7 years (IQR 1.2–2.4) and Kaplan-Meier post-LT survival at 1, 2, and 3 years was 100%, 95.0%, and 83.1%, respectively. HCC recurrence has developed in 5 patients (7.9%) to date with median time from LT to recurrence of 16.8 months (IQR 9.7–22.3). In exploratory analysis, time from successful down-staging to LT was not associated with HCC recurrence. Overall Kaplan-Meier intention-to-treat survival at 1 and 3 years from first down-staging procedure was 92.5% and 73.0%, respectively with no significant difference found when comparing TACE and Y-90 as type of first LRT received. Stratified by initial tumor burden, intention-to-treat survival at 1 and 3 years from first LRT was 96.7% and 72.9%, respectively, in those with total tumor diameter <6 cm compared to 91.3% and 72.6% for total tumor diameter >7 cm (p=0.52) (Figure 4).

DISCUSSION

In this first multicenter prospective study on tumor down-staging from the MERITS-LT consortium (7 centers from 4 UNOS regions) designed to evaluate the outcomes of down-staging based on UNOS-DS criteria, we observed a very high overall probability of successful down-staging to within Milan criteria in 83% of the patients. The cumulative probabilities of successful down-staging was 68% at 6 months, and 83% and 88% at 1 and 2 years, respectively, after the first down-staging treatment. About two-thirds were successfully down-staged after a single LRT. The only factor predicting successful down-staging was tumor burden measured by the sum of the largest tumor diameters. Even those with a total tumor diameter > 7 cm had an 81% probability of successful down-staging (versus 88% for those with total tumor diameter < 6 cm). These findings validate the feasibility of down-staging on a broad scale under the current UNOS-DS guidelines, and highlight the importance of setting upper limits in the tumor burden to ensure a high down-staging success rate. Relaxing the eligibility criteria on initial tumor burden would result in a significantly lower down-staging success rates (16, 26, 27) and potentially worse post-LT outcomes (26, 28). Sinha et al (26) reported an 84% rate of successful down-staging to Milan criteria in those meeting UCSF/UNOS-DS criteria, similar to the rate reported in the current study, versus a significantly lower success rate of 65% in the “all-comers” group with initial tumor burden beyond these criteria and without upper limits. There was also a strong correlation between the sum of tumor number and largest tumor diameter

and the likelihood of successful down-staging. The cumulative probability of successful down-staging at 1 year from time of first LRT decreased incrementally with a greater sum of the tumor number and largest tumor diameter, and fell below 50% in those with a sum of 12 or greater (26).

A lesson learned from this and prior experience with down-staging is to restrict down-staging to only patients with adequate hepatic functional reserve. It has been proposed that only patients with Child's A or B cirrhosis with a total bilirubin ≤3 mg/dL should undergo tumor down-staging to ensure an acceptably low risk for post-treatment hepatic decompensation (15). In the present study, we allowed enrollment of those with total bilirubin up to 4 mg/dL. In principle, patients who develop hepatic decompensation following LRT before achieving successful down-staging are not eligible for LT. In the present study, 97% of patients had Child's A or B cirrhosis. The median Child-Pugh score was 6 and the median MELD score of 9 in our cohort. Improved selection of patients with good liver function might have contributed to the higher down-staging success rate in this study when compared to previous reports on down-staging using the same tumor criteria for inclusion (17, 18).

It is important to point out that the present study followed a number of recently implemented UNOS guidelines - a minimal wait time of 6 months from successful down-staging to LT, and exclusion of patients with AFP ≥ 1000 ng/mL from priority listing for LT unless there is a significant reduction of AFP to < 500 ng/mL with LRT (20). Under these guidelines, the cumulative probability of dropout due to tumor progression or liver-related death was 22.5% at 1 year and 37.3% at 2 years. Baseline AFP was not associated with the probability of successful down-staging or dropout, although there was a trend for an AFP ≥100 ng/ml to be associated with a higher risk of dropout. A baseline AFP ≥ 1000 ng/mL was not a predictor of a lower rate of successful down-staging or a higher risk of dropout, even though 12% of our cohort had baseline AFP > 1000 ng/mL and required a reduction to < 500 ng/mL with LRT to be considered for LT. In contrast, a previous study from UCSF (17) found a baseline AFP of ≥ 1000 ng/mL to be associated with a 2.4 fold increased risk of wait-list dropout after down-staging. Similarly, a study from Region 5 demonstrated an AFP of > 1000 ng/mL to be a significant predictor of treatment failure, defined as dropout, liver-related death without LT or HCC recurrence after LT (18). The exclusion of Child's B or C patients with baseline AFP > 1000 ng/mL from enrollment into this study is a possible explanation for this discrepancy. While AFP is required in all patients at baseline and every 3 months while on the LT waiting list, not all of the study population had other biomarkers including AFP-L3, DCP and NLR obtained at baseline. Within these limitations, AFP-L3 ≥10% was the only factor independently associated with waitlist dropout. Although there is a potential role for AFP-L3, DCP and NLR as prognostic markers in LT (29–33), more prospective studies are needed to help define the place of these biomarkers in clinical practice (34).

We also sought to assess the influence of the type of initial trans-arterial tumor treatment on down-staging outcomes. Over 90% of the cohort received either TACE (n=132) or Y-90 (n=62) as initial down-staging treatment. When comparing these two treatment modalities, pre-treatment AFP and total tumor diameter were similar and there were no observed differences in mRECIST response, probability of or time to successful down-staging, or

probability of waitlist dropout or LT. Similarly, a systematic review and pooled analysis by Parikh et al (16) showed no difference in rate of successful down-staging between Y-90 and TACE, although there was only one study comparing these two treatment modalities. In the present study, fewer LRT were required for patients initially treated with Y-90 than those receiving TACE (median 2 (IQR 1–3) for Y-90 vs 3 (IQR 2–5) for TACE). This finding mirrors that of the PREMIERE trial (35), a small single-center phase II randomized trial which showed a significantly longer time to progression with Y-90 compared to TACE but only 10 patients had tumors initially exceeding Milan criteria. Although not statistically significant, we observed a higher rate of complete pathologic response and a lower probability of tumor under-staging and microvascular invasion in the explant in those initially receiving Y-90. Until a large multi-center randomized trial comparing Y-90 and TACE is undertaken, the choice between these modalities as initial down-staging treatment will depend on center expertise and remain a matter of debate.

We observed excellent post-LT survival of 100% at 1 year and 95% at 2 years, but the follow-up was too short for post-LT outcomes to be the primary objective of this study. On a cautionary note, over 40% had tumor under-staging to beyond Milan criteria in the explant, which was at least 2 times higher than that in earlier studies from Region 5 (17, 18), but in line with that from several recent analyses of UNOS database (28, 36). In one study by Mehta et al. (28), one-third of HCC patients initially meeting UNOS down-staging criteria had tumor beyond Milan criteria on explant. In another study by Mahmud and colleagues using the UNOS explant pathology form (36), tumor under-staging in the explant was associated with increased post-LT HCC recurrence and death, and the risk of tumor-under-staging was higher among those requiring tumor down-staging before LT. Multiple explant-based prognostic models also demonstrated worse post-LT survival related to tumor under-staging beyond Milan criteria in the explant (32, 37, 38). These findings underscore the importance of strict adherence to down-staging definitions and ensuring adequate response to down-staging prior to LT, in addition to finding ways to reduce inaccuracies in radiographic staging assessments. It has been shown that in patients who require tumor down-staging, the higher the tumor burden on the last imaging study prior to LT, the greater the risk of under-staging on explant pathology. The odds of tumor under-staging on explant increases by 10% for each 1-cm increase in total tumor diameter on the last pre-LT imaging study (28). Similarly, in the present study, the only factor associated with explant under-staging to beyond Milan criteria was the sum of the number of lesions plus largest tumor diameter on the last imaging prior to LT. The odds of under-staging increased by 35% per 1 unit increase in this sum. Based on these observations, we should consider down-staging to within Milan criteria as the minimal requirement for LT, and perform additional LRT to further reduce the viable tumor burden and ideally to achieve complete tumor necrosis prior to LT (19).

One of the strengths of this study is the prospective multi-center study design to investigate the outcomes of down-staging in a large cohort from 4 broad geographic regions using uniform inclusion criteria and endpoints of down-staging. Furthermore, the study period from 2016 to 2019 ensures no overlap of patients included in previous publications from several participating centers (17, 18). There are also limitations, mainly the short duration of post-LT follow-up in a relatively small number of patients receiving LT to date. The

primary objective of this study is to evaluate the feasibility of successful down-staging and waitlist outcomes. It will take another 2 to 3 years to report long-term post-LT survival and HCC recurrence data to confirm the efficacy of tumor down-staging. We originally sought to include three additional LT centers from two more UNOS regions to increase the study's power and applicability. However, these centers were unable to provide data and were therefore removed from the consortium. This study was performed prior to the recent implementation of median MELD at LT minus 3 points for organ allocation for HCC. Consequently, this study could not account for the potential impact of such policy change on wait list outcome and access to LT in down-staged patients. These effects should be analyzed in future studies. Patients in all participating centers are eligible to receive both TACE and Y-90 radioembolization, although center-specific differences in the type of first LRT for down-staging still exist. Specifically, the proportion undergoing TACE as initial LRT (compared to Y-90) at the 7 centers ranges from 36% to 90%. This may be viewed as a "real world" experience and the type of initial LRT does not appear to have a significant impact on all the primary endpoints. Finally, there is the possibility of a referral bias as patients within down-staging criteria who received LRT in the community but experienced subsequent disease progression might not have ever been referred for LT.

In conclusion, in this first prospective multi-regional study based on UNOS-DS criteria, we observed a >80% probability of initial down-staging with relatively low likelihood of subsequent tumor progression, and validated the feasibility of down-staging on a broad scale under the current UNOS-DS guidelines. We found similar efficacy of TACE and Y-90 as initial down-staging treatment. Despite excellent 1- and 2-year post-LT survival, the tumor under-staging rate was higher than expected. A point of emphasis is the critical importance of precise tumor staging definitions in achieving good outcomes (19). Since pre-LT viable tumor burden strongly correlates with the risk of tumor under-staging, we advocate down-staging to within Milan criteria as merely a minimal requirement for LT, and performing additional LRT until complete tumor necrosis is achieved prior to LT.

Acknowledgments

Grant Support: This work is supported in part by a grant from the National Institute of Health to the University of California, San Francisco Liver Center (P30 DK026743)

Disclosures: Neil Mehta has served on advisory boards for WAKO Diagnostics and has received institutional research funding from Wako Diagnostics, Glycotest, and Target Pharmasolutions. Maarouf Hoteit has served on advisory boards for Eisai and Hepquant. Neehar Parikh serves as a consultant for Bristol Myers-Squibb, Exact Sciences, Eli Lilly, and Freenome and has served on advisory boards for Genentech, Eisai, Bayer, Exelixis, and Wako Diagnostics. He has received institutional research funding from Bayer, Target Pharmasolutions, Exact Sciences, and Glycotest. Francis Yao has received institutional research funding from Wako Diagnostics. None of the other authors have any relevant potential conflicts of interest to disclose.

Abbreviations:

LT	liver transplantation
HCC	hepatocellular carcinoma
LRT	local regional therapy

UCSF	University of California, San Francisco
UNOS	United Network for Organ Sharing
OPTN	Organ Procurement and Transplantation Network
UNOS-DS	UNOS down-staging protocol
MELD	Model for End Stage Liver Disease
LI-RADS	Liver Imaging Reporting and Data System
CT	computed tomography
MRI	magnetic resonance imaging
TACE	trans-arterial chemoembolization
Y-90	Yttrium-90
HR	hazard ratio
sHR	subhazard ratio
IQR	interquartile range
AFP	alpha-fetoprotein
AFP-L3	lectin-reactive alpha-fetoprotein
DCP	des-gamma carboxyprothrombin
NLR	neutrophil to lymphocyte ratio

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Background & Context

UNOS down-staging (DS) protocol has been adopted for priority listing for liver transplant (LT) though no national studies have confirmed the feasibility of down-staging or the optimal therapy to achieve successful down-staging.

New Findings

Successful down-staging to within Milan criteria exceeded 80% with similar efficacy of TACE and Y-90 as initial treatment. While rates of explant under-staging were relatively high, 2-year post-LT survival was 95%.

Limitations

Short post-LT follow-up in a relatively small sample of LT recipients and the possibility of referral bias.

Impact

This study validates the feasibility of down-staging on a broad scale under the current UNOS-DS guidelines.

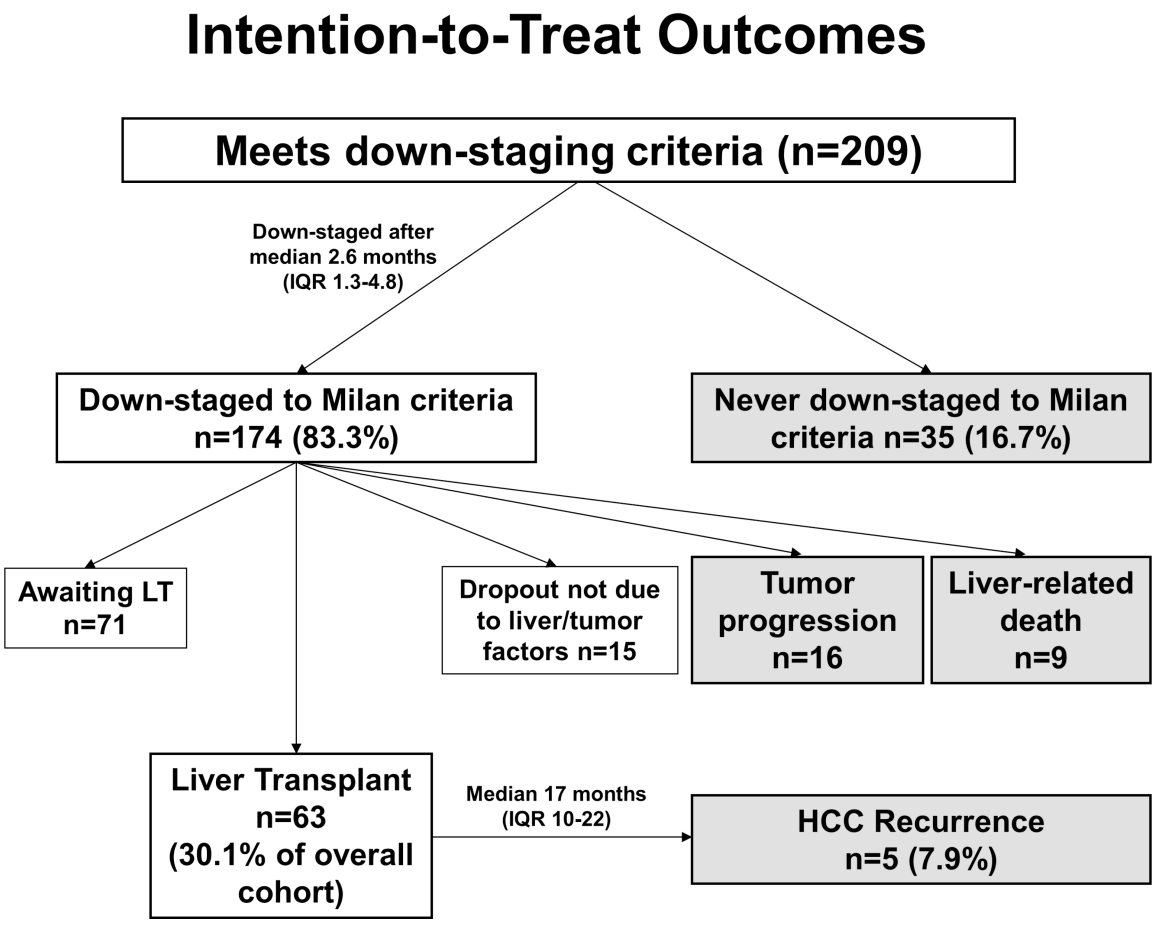

Figure 1.
Summary of the intention-to-treat outcome of the 209 patients enrolled in the prospective down-staging protocol

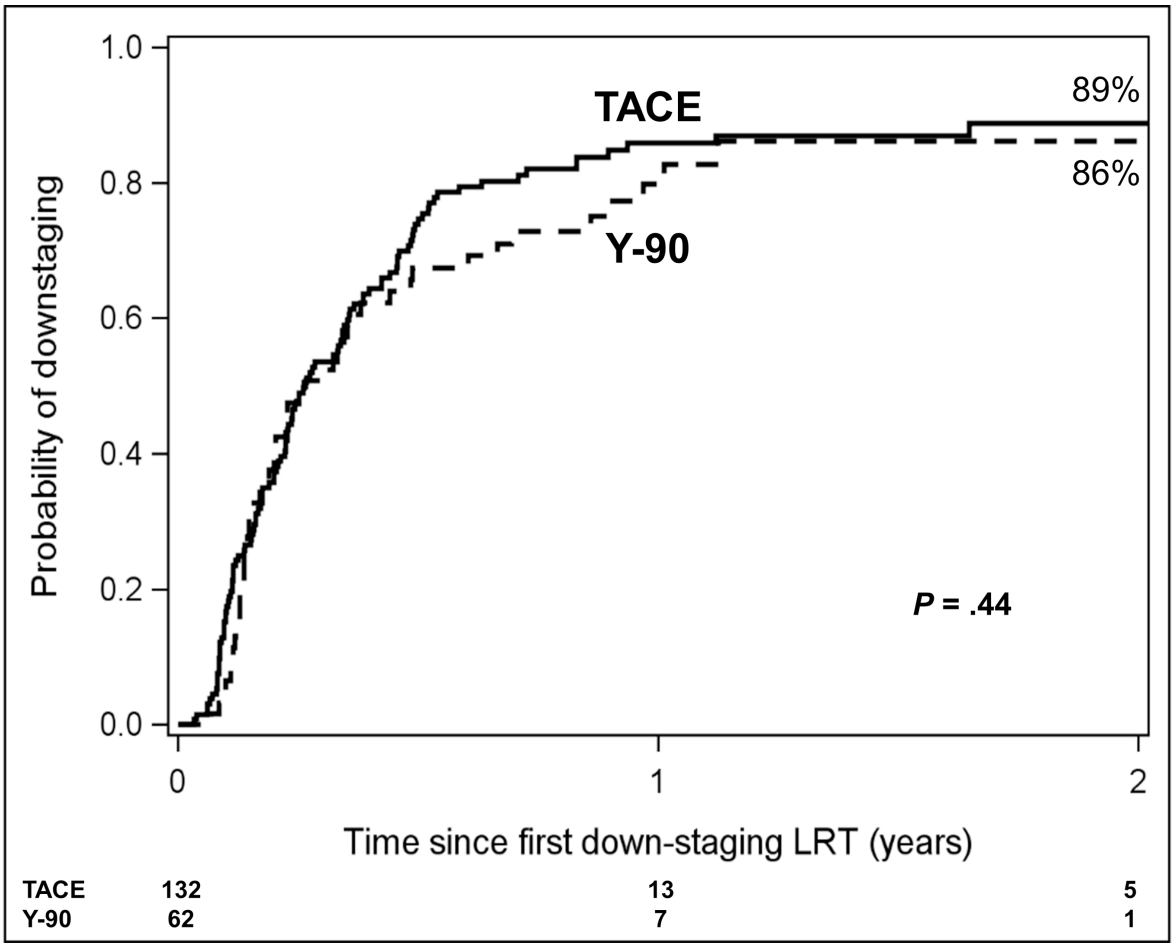

Figure 2.
Kaplan-Meier probability of successful down-staging by type of first local-regional therapy (TACE versus Y-90)

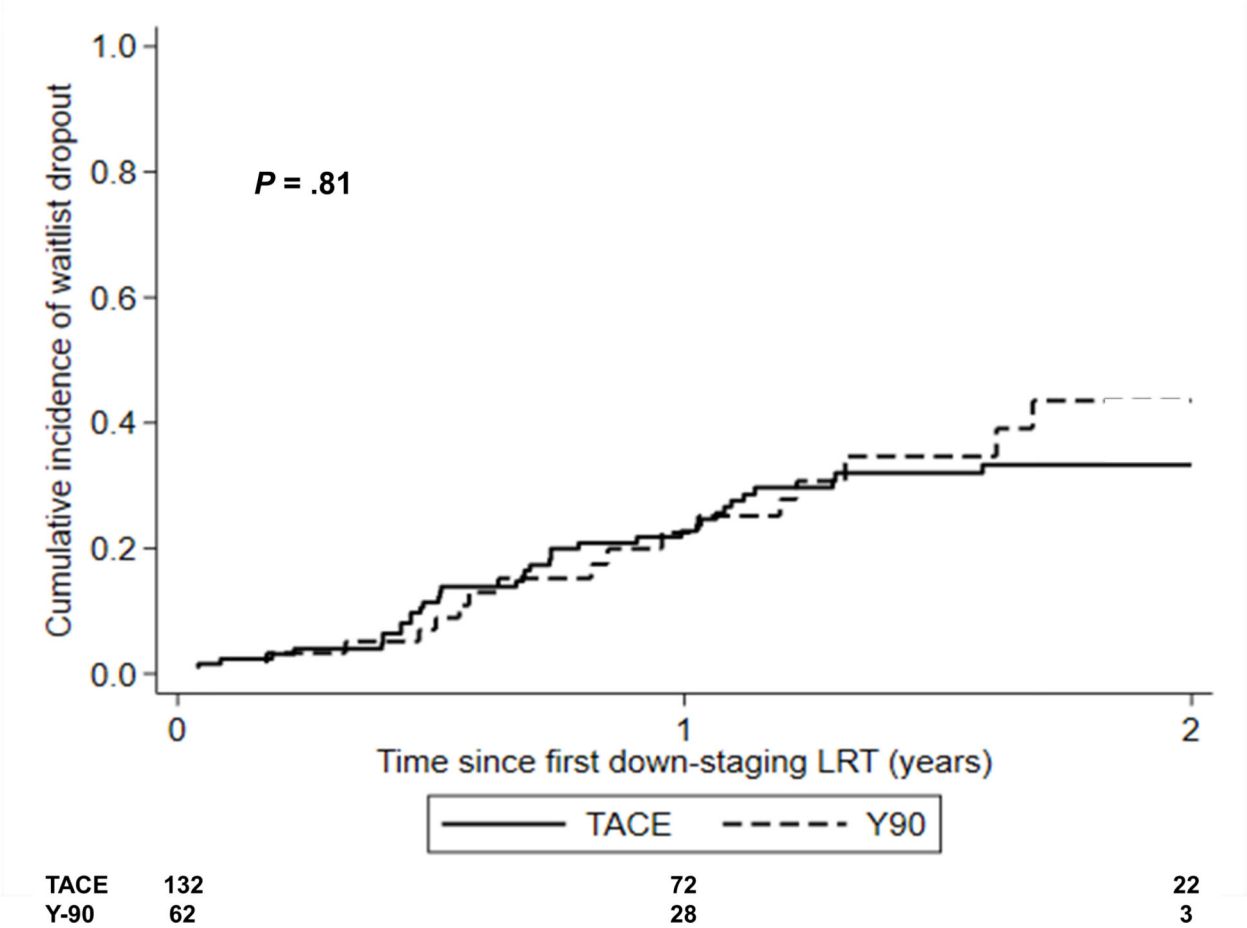

Figure 3.
Kaplan-Meier probability of protocol dropout from date of first down-staging treatment

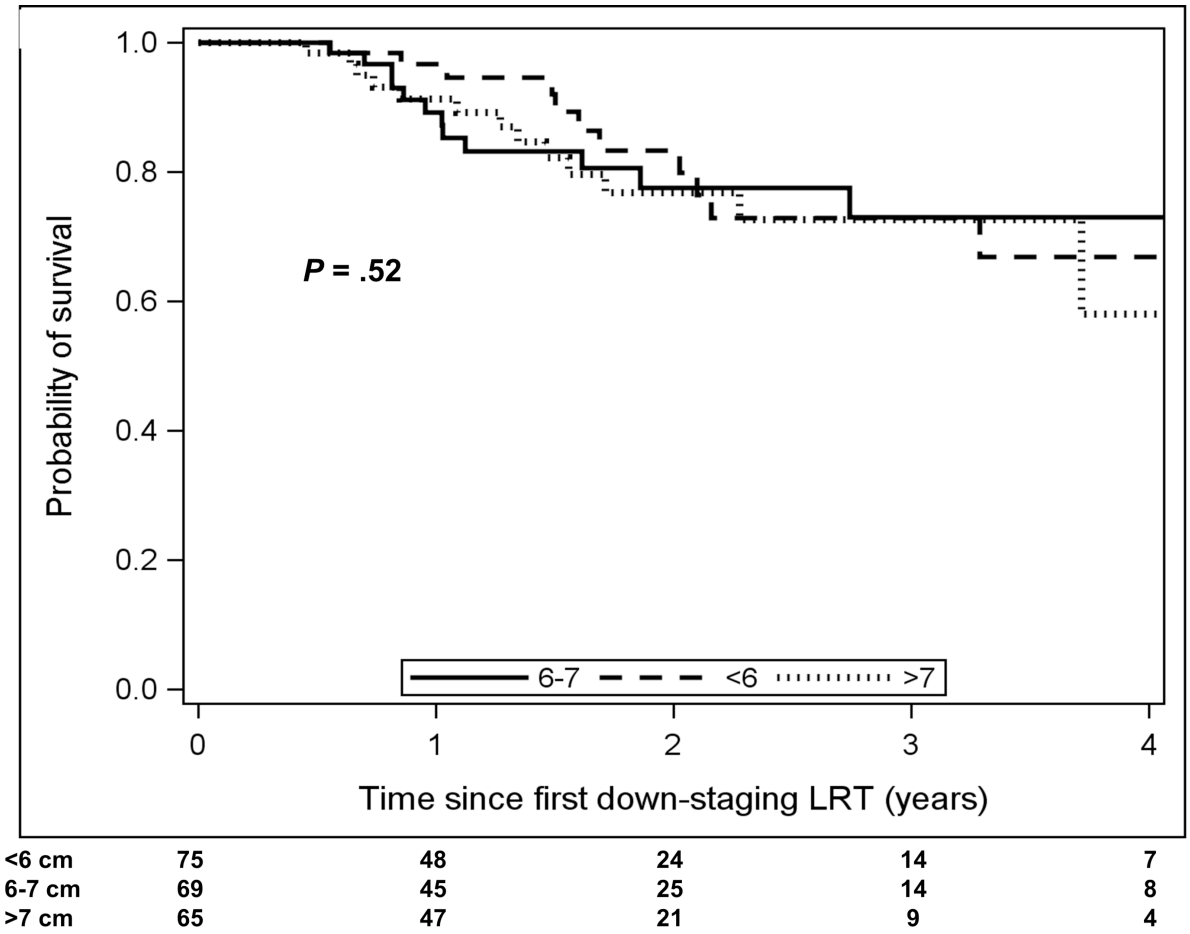

Figure 4.

Kaplan-Meier probability of intention-to-treat survival from first down-staging treatment stratified by initial total tumor burden

Table 1.

United Network for Organ Sharing (UNOS) Down-staging Protocol

Inclusion Criteria
HCC exceeding Milan criteria but meeting one of the following: 1. Single lesion 5.1–8 cm 2. 2–3 lesions each ≤ 5 cm with the sum of the maximal tumor diameters ≤ 8 cm 3. 4–5 lesions each ≤ 3 cm with the sum of the maximal tumor diameters ≤ 8 cm Plus absence of vascular invasion or extra-hepatic disease based on cross-sectional imaging
Criteria for Successful Down-staging
Residual tumor size and diameter within Milan criteria (1 lesion ≤5 cm, 2–3 lesions ≤3 cm) a) Only viable tumor(s) are considered; tumor diameter measurements should not include the area of necrosis from tumor directed therapy b) If there is more than one area of residual tumor enhancement, then the diameter of the entire lesion should be counted towards the overall tumor burden
Criteria for Down-staging Failure and Exclusion from Liver Transplant
1. Progression of tumor(s) to beyond inclusion/eligibility criteria for down-staging (as defined above) 2. Tumor invasion of a major hepatic vessel based on cross-sectional imaging 3. Lymph node involvement by tumor or extra-hepatic spread of tumor 4. Infiltrative tumor growth pattern 5. Per current UNOS policy, if AFP ≥ 1000 ng/mL then transplant cannot be undertaken unless AFP level decreases to < 500 ng/mL with local-regional therapy
Timing of Liver Transplant in Relation to Down-staging
1. There should be a minimum observation period of 3 months of disease stability from successful down-staging to LT 2. Per current UNOS policy, patient must remain within Milan criteria for 6 months after successful down-staging before receiving MELD exception points

Table 2.

Baseline and Tumor Treatment Characteristics of the Down-staging Group

Study Variable	Overall (n=209)
Median Age (IQR)	63 (58–67)
Male (%)	178 (85.2)
Race/Ethnicity (%) Caucasian Hispanic Asian African American	 123 (60.0) 45 (22.0) 23 (11.2) 10 (4.9)
Liver Disease Etiology (%) Hepatitis C Alcohol NAFLD Hepatitis B Other	 125 (59.8) 33 (15.8) 23 (11.0) 16 (7.7) 12 (5.7)
Median CTP Score (IQR) * Child's A (CTP 5–6, %) Child's B (CTP 7–9, %) Child's C (CTP 10–15, %)	6 (5–6) 151 (75.5) 43 (21.5) 6 (3.0)
Median MELD (IQR)	9 (7–11)
Median AFP ng/mL (IQR) >100 (%) ≥1000 (%)	13 (5–74) 48 (23.0) 24 (11.5)
Median AFP-L3% (IQR) **	10.3 (4.6–16.9)
Median DCP (IQR) **	2.5 (0.5–19.9)
Median NLR (IQR)	2.5 (1.7–3.8)
Median PLR (IQR)	86.3 (66.0–117.4)
Number of HCC Lesions 1 lesion 2–3 lesions 4–5 lesions	 67 (32.1) 113 (54.1) 29 (13.9)
Initial Total Tumor Diameter (cm) (IQR)	6.2 (5.6–7.3)
Number LRT Received (%) 1 2 3 4 ≥5	 44 (21.1) 53 (25.4) 41 (19.6) 25 (12.0) 46 (22.0)
Type of LRT Received (%) Received 1+ TACE Received 1+ Y-90 Received 1+ Ablation	 169 (80.9) 84 (40.2) 59 (28.2)
Type of 1st LRT Received (%) TACE	132 (63.1) 62 (29.7)
Y-90 Other	15 (7.2)

* n=200

** n=83

Abbrevations: CTP, Child-Turcotte-Pugh; AFP-L3%, DCP, des-gamma carboxyprothrombin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LRT, local-regional therapy; TACE, transarterial chemoembolization; Y-90, Yttrium-90 radioembolization

Table 3.

Clinical Characteristics and Outcomes by Type of 1st Down-staging Treatment

Variable	TACE (n=132)	Y-90 (n=62)	p-value
Median Age (IQR)	63 (58–67)	63 (60–66)	0.65
Male (%)	122 (92.4)	45 (72.6)	<0.001
CTP Class (%) *			0.16
Child's A	91 (72.2)	50 (80.6)	
Child's B	29 (23.0)	12 (19.4)	
Child's C	6 (4.8)	0	
Median MELD (IQR)	9 (7–12)	8.5 (7–10)	0.04
Median AFP ng/mL (IQR)	11.7 (4.9–58.0)	17.9 (5.7–238.4)	0.11
Number of HCC Lesions			0.003
1 lesion	32 (24.2)	30 (48.4)	
2–3 lesions	80 (60.6)	25 (40.3)	
4–5 lesions	20 (15.2)	7 (11.3)	
Initial Total Tumor Diameter (cm) (IQR)	6.3 (5.6–7.3)	6.3 (5.8–7.3)	0.67
# Lesions Treated with 1st LRT (IQR)	1 (1–2)	1 (1–2)	0.07
mRECIST Response to 1st LRT			0.67
Complete Response	37 (28.0)	17 (27.4)	
Partial Response	69 (52.3)	30 (48.4)	
Stable Disease	14 (10.6)	7 (11.3)	
Progressive Disease	12 (9.1)	8 (12.9)	
Median #LRT Received (IQR)	3 (2–5)	2 (1–3)	0.006
Ever Down-Staged (%)	113 (85.6)	50 (80.6)	0.38
Time to Down-Staged (mo) (IQR)	2.9 (1.3–5.6)	2.4 (1.7–4.6)	0.73
Down-Staging Protocol Dropout (%)	48 (36.4)	20 (32.3)	0.58
Time to Dropout (mo) (IQR)	8.4 (5.8–13.0)	10.2 (6.6–14.7)	0.33
LT (%)	44 (33.3)	14 (22.6)	0.18 0.19
Time to LT (mo) (IQR)	18.3 (10.8–25.2)	15.9 (11.2–19.2)	0.18
AFP prior to LT (IQR)	4.3 (3.0–21.7)	9.2 (6.0–16.0)	
Explant Pathology (%)			
Completely Necrotic Tumor(s)	9 (20.5)	4 (30.8)	0.76
Beyond Milan	19 (43.2)	3 (23.1)	0.44
Explant Microvascular Invasion	9 (20.5)	1 (7.7)	0.29

* n=188

Abbrevations: TACE, transarterial chemoembolization; Y-90, Yttrium-90 radioembolization; CTP, Child-Turcotte-Pugh; LRT, local-regional therapy; LT, liver transplantation